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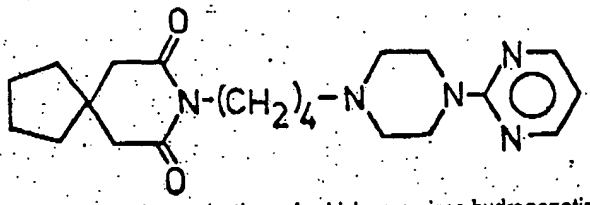
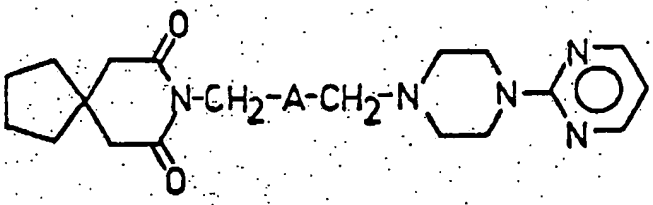
(54) 4-(2-Pyrimidinyl)-piperazine derivatives

(57) The invention relates to a new and improved process for the preparation of 8-[4-[4-(2-pyrimidinyl)--1-piperazinyl]-butyl]-8-aza-spiro[4.5]decane-7, 9--dione of the Formula I



(I)

and pharmaceutically acceptable acid addition salts thereof, which comprises hydrogenating a compound of the general Formula II



(II)

(wherein A stands for -C≡ C- or CH=CH-) and, if desired, converting the compound of the Formula I thus obtained into a pharmaceutically acceptable acid addition salt thereof.

The compound of the Formula I is a known anxioselective agent.

The invention also relates to intermediates of Formula II used in the above process and a method for the preparation thereof. These compounds also have anxioselective action.

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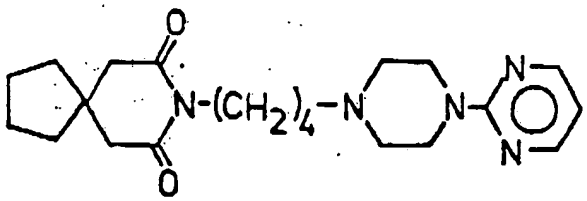
PIPERAZINE DERIVATIVES AND PROCESS FOR THE PREPARATION THEREOF

This invention relates to a new and improved process for the preparation of pharmaceutically active piperazine derivatives and to new intermediates useful in the preparation thereof and also to a process for the preparation of the said intermediates.

According to an aspect of the present invention there is provided a process for the preparation of the therapeutically active known 8-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-8-aza-1-spiro[4.5]-decane-7,9-dione of the Formula I.



(I)

It is known that the 8-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-8-aza-spiro[4.5]decane-7,9-dione of the Formula I possesses valuable anxioselective properties (UK Patent No. 1,332,194). In prior art several methods are disclosed for the preparation of the compound of the Formula I.

According to UK patent No. 1,332,194 the compound of the Formula I is prepared by reacting 8-oxa-spiro[4.5]decane-7,9-dione with 1-(4-aminobutyl)--4-(2'-pyrimidinyl)-piperazine. The reaction is accomplished in pyridine at the boiling point of the reaction mixture. The desired compound of the Formula I is obtained in crude form with medium yield. The crude product is purified in the free base form by crystallization or fractional distillation in vacuo. The drawback of the above first purification method is that the losses are significant while fractional distillation in vacuo is carried out at high temperature (240-265 °C) under low pressure (13.3 Pa), which constitutes a severe thermal load and leads to decomposition of the product.

According to an other method disclosed in UK patent No. 1,332,194 8-(4-chlorobutyl)-8-aza-spiro-[4.5]decane-7,9-dione is reacted with N-(2-pyrimidinyl)--piperazine in the presence of sodium carbonate in n--butanol at the boiling point of the reaction mixture for 3 days. The extremely long reaction time makes the process unsuitable for economical industrial scale manufacture. A further disadvantage is that the product can be purified but with the aid of complicated and circumstantial methods. A still further drawback resides in the fact that the 1-bromo-4-chloro-butane used as starting material in the preparation of 8-(4-chlorobutyl)-8-aza-spiro[4.5]decane-7,9-dione is very difficult to obtain and which can be prepared

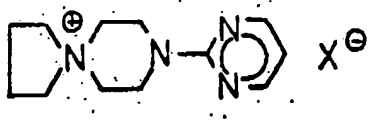
only by means of complicated methods.

According to a still further process disclosed in UK patent No. 1,332,194 8-oxa-spiro[4.5]-decane-7,9-dione is first converted into 8-aza-spiro-[4.5]decane-7,9-dione. The 1-(4-chlorobutyl)-4-(2-pyrimidinyl)-piperazine prepared from N-(2-pyrimidinyl)-piperazine and 1-bromo-4-chloro-butane is reacted with 8-aza-spiro[4,5]decane-7,9-dione. This process comprises several steps which are very delicate and can be carried out only under serious difficulties. The compound of the Formula I thus obtained is suitable for pharmaceutical purposes only after severalfold purification. A further drawback resides in the poor availability of the 1-bromo-4-chloro-butane used as starting material.

The 1-(4-aminobutyl)-4-(2-pyrimidinyl)-piperazine can be prepared by reacting 1-(2-pyrimidinyl)-piperazine with 3-chloropropionitrile in n-butanol as medium at the boiling point of the reaction mixture for a longer period of time (the reaction time is 16 hours). The intermediate thus obtained must be subjected to purification by crystallization (yield 70 %). The intermediate nitrile is catalytically hydrogenated under pressure with a yield of about 70 % (UK patent No. 1,332,194).

In Hungarian patent No. 187,999 a further process is set forth. The compound of the Formula I is prepared as follows: from 1-(4-chlorobutyl)-4-(2-pyrimidinyl)-piperazine first the spiro quaternary

ammonium piperazine derivative of the Formula IX



(IX)

is prepared which is reacted with 8-aza-spiro[4,5]-decane-7,9-dione in the presence of a strong base. This process is accompanied by a number of drawbacks. Thus the yield is low, the synthesis is a multistep process and the contaminated product obtained can only be purified with difficulty.

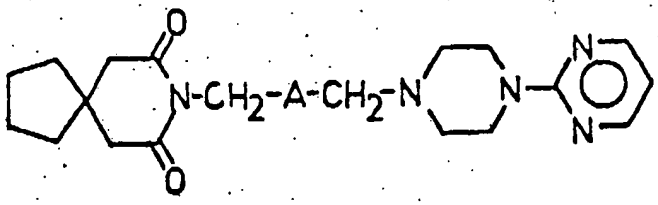
According to Swiss patent No. 647,518 8-aza-spiro[4.5]decane-7,9-dione is first reacted with 1,4-dibromo-butane, the 4-bromo-butyl derivative thus obtained is treated with piperazine, whereupon the product thus obtained is reacted with 2-chloro--pyrimidine. The object of this process is to prepare a compound labelled with ^{14}C isotope and is therefore but of theoretical importance.

According to Spanish patent No. 536,286 the potassium salt of 8-aza-spiro[4.5]decane-7,9-dione is reacted with 4-chloro-butyraldehyde, whereupon the product thus obtained is reacted with N-(2--pyrimidinyl)-piperazine under reductive conditions. This process is of mere academical significance too and is unsuitable for industrial scale manufacture.

It is the object of the present invention to provide a process which overcomes the drawbacks

of the above known methods and enables the favourable preparation of the compound of the Formula I on industrial scale too by using readily available starting materials. It is a further object of the present invention to provide a process which gives the desired compound of the Formula I with good yields and in high purity.

According to the present invention there is provided a process for the preparation of 8-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-8-aza-spiro[4.5]-decane-7,9-dione of the Formula I and pharmaceutically acceptable acid addition salts thereof, which comprises hydrogenating a compound of the general Formula II

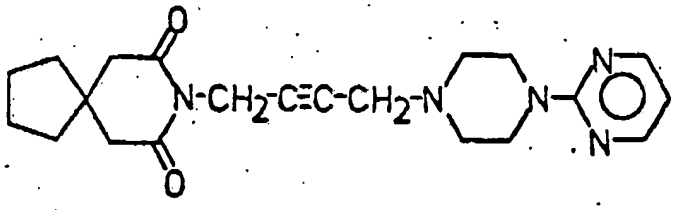


(II)

(wherein A stands for -C≡C- or -CH=CH-) and, if desired, converting the compound of the Formula I thus obtained into a pharmaceutically acceptable acid addition salt thereof.

According to a form of realization of the process of the present invention the compound of the Formula IIA is hydrogenated. The reaction may be performed in the presence of a metal catalyst with hydrogen. As catalyst preferably palladium or Raney-nickel can be used. One may particularly advantageously

proceed by carrying out hydrogenation in the presence of a palladium catalyst applied onto a charcoal carrier. Hydrogenation of the compound of the Formula IIA



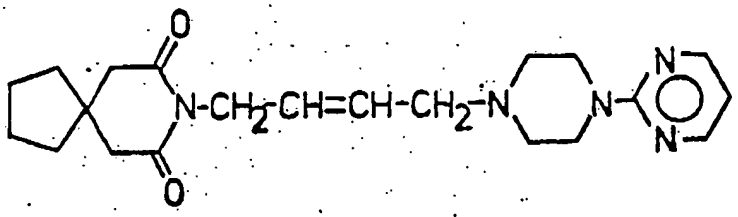
(IIA)

can be accomplished in an inert organic solvent. As reaction medium preferably lower aliphatic alcohols - particularly methanol or ethanol - can be used. Hydrogenation may be carried out preferably under atmospheric pressure at room temperature.

The compound of Formula I can be isolated from the reaction mixture by known methods. Thus one may proceed by removing the catalyst by filtration and evaporating the filtrate. The catalyst can be re-introduced into the hydrogenation cycle directly without further treatment.

The compound of the Formula I thus obtained is of high purity and is suitable for pharmaceutical use without any special purification.

According to an other form of realization of the process of the present invention the compound of the Formula IIB



(IIB)

is reduced. The reaction can be performed by catalytic hydrogenation. As metal catalyst preferably palladium can be used. The reaction may be carried out in an inert organic solvent. As reaction medium preferably lower aliphatic alcohols - particularly methanol or ethanol - can be used. Hydrogenation of the compound of the Formula IIB can be accomplished preferably under atmospheric pressure at room temperature.

The compound of the Formula I thus obtained can be converted into an acid addition salt thereof by known methods. Any pharmaceutically suitable inorganic acid (e.g. hydrochloric acid, hydrogen bromide, sulfuric acid, nitric acid etc.) or organic acid (e.g. maleic acid, fumaric acid, lactic acid, malic acid, tartaric acid, succinic acid etc.) can be used.

The starting materials of the general Formula II are new compounds.

According to a further aspect of the present invention there are provided new compounds of the general Formula II (wherein A stands for -C≡C- or -CH=CH-).

Thus the following new compounds are provided: 8-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-but-2-inyl}-8--aza-spiro[4.5]decane-7,9-dione of the Formula IIA;

8-{4-[4-(2-pyrimidinil)-1-piperazinyl]-butene-2-yl}-8-aza-spiro[4.5]decane-7,9-dione of the Formula IIB.

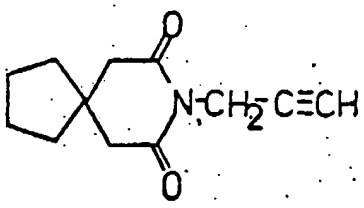
The compounds of the general Formula II are, on the one hand, useful intermediates suitable for the preparation of the therapeutically active known compound of the Formula I while, on the other hand, possess valuable pharmaceutical properties per se.

According to a further feature of the present invention there are provided pharmaceutical compositions comprising as active ingredient a compound of the general Formula II (wherein A is as stated above) or a pharmaceutically acceptable acid addition salt thereof in admixture with suitable inert carriers.

The pharmaceutical compositions of the present invention can be prepared by known methods of pharmaceutical industry and contain conventional pharmaceutical carriers and auxiliary agents.

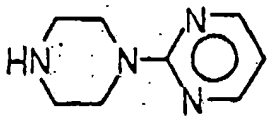
According to a still further feature of the present invention there is provided a process for the preparation of compounds of the general Formula II (wherein A stands for -C≡C- or -CH=CH-) and acid addition salts thereof, which comprises

a) for the preparation of the compound of the Formula IIA, subjecting the propine derivative of the Formula III



(III)

to Mannich condensation with an amine of the Formula IV;



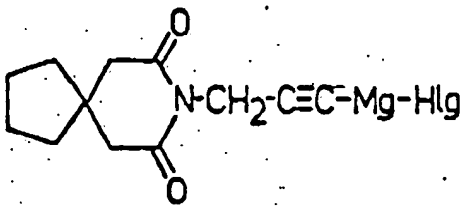
(IV)

or

b) for the preparation of the compound of the Formula IIA, reacting the propine derivative of the Formula III with an alkyl magnesium halide of the general Formula V

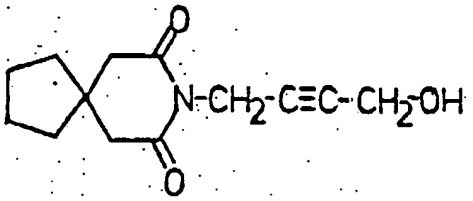
R-Mg-Hlg (V)

(wherein R stands for C_{1-4} alkyl and Hlg is chlorine, iodine or bromine), reacting the compound of the general Formula VI



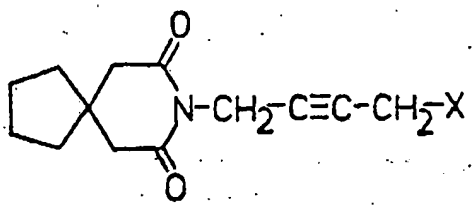
(VI)

thus obtained (wherein Hlg is as stated above) with at least one molar equivalent amount of trioxymethylene or formaldehyde, converting the substituted amino alcohol of the Formula VII



(VII)

into a reactive ester of the general Formula VIII



(VIII)

(wherein X stands for a reactive ester group) and reacting the compound of the general Formula VIII thus obtained with a piperazine derivative of the Formula IV; or

c) for the preparation of the compound of the Formula IIB, subjecting the compound of the Formula IIA to partial hydrogenation;

and, if desired, converting a compound of the general Formula II thus obtained into an acid addition salt thereof or setting free the base from an acid addition salt.

According to method a) the compound of the Formula IIA is prepared by subjecting the propine derivative of the Formula III to Mannich condensation with an amine of the Formula IV. The Mannich condensation is carried out by methods known per se [Calvin A. Buehler, Donald E. Pearson: Survey of Organic Syntheses (USA 1970) Vol. 1, page 465]. One may proceed preferably be using formaldehyde in the form of paraformaldehyde. The reaction may be accomplished preferably under heating, particularly at the boiling point of the reaction mixture. The reaction may be carried out in an inert organic solvent. As reaction medium preferably an ether (e.g. diethyl ether, dioxane or tetrahydrofurane) can be used. From the reaction mixture the compound of the Formula IIA can be isolated in a known manner (e.g. by extraction with a suitable organic solvent).

In the first step of method b) the propine derivative of the Formula III is reacted with an alkyl magnesium halide of the general Formula V. R stands for a straight or branched chain alkyl group having 1-4 carbon atoms (e.g. methyl, ethyl, n-propyl, isobutyl etc.). As compound of the general Formula V preferably methyl magnesium iodide, methyl magnesium bromide, methyl magnesium chloride, ethyl magnesium iodide, ethyl magnesium chloride or ethyl magnesium bromide can be used. The reaction of the compounds of the general Formula III and V can be accomplished preferably in anhydrous ethereal medium under heating.

The compound of the general Formula VI thus obtained is reacted - preferably without isolation - with at least a molar equivalent amount of trioxymethylene or paraformaldehyde. It is preferred to use gaseous formaldehyde. The trioxymethylene or formaldehyde is preferably used in an amount of 1 - 1.1 moles - particularly 1.0 - 1.05 moles - related to 1 mole of the compound of the general Formula VI. The reaction may be carried out preferably under heating. The compound of the general Formula VII can be isolated by evaporating the etheral solution.

The compound of the Formula VII thus obtained is converted into an ester of the general Formula VIII by methods known per se. X stands preferably for halogen (e.g. chlorine, bromine or iodine), alkylsulfonyloxy (e.g. methanesulfonyloxy) or arylsulfonyloxy (e.g. phenylsulfonyloxy, p-bromophenylsulfonyloxy, p-toluene-sulfonyloxy etc.). One may preferably proceed by reacting the compound of the Formula VII with p-toluene-sulfonyl chloride. The reaction may be carried out at room temperature or under slight warming.

The compound of the general Formula VIII thus obtained is reacted - without or after isolation, preferably directly without isolation - with a piperazine derivative of the general Formula IV. The reaction may be accomplished in a manner known per se. The reaction may be preferably carried out in an

inert organic solvent. As reaction medium e.g. aromatic hydrocarbons (e.g. benzene, toluene, xylene etc.) can be used. The reaction may be preferably performed under heating, particularly at the boiling point of the reaction mixture.

The compound of the general Formula IIA thus obtained can be isolated in a manner known per se (e.g. by evaporating the reaction mixture).

According to method c) the compound of the Formula IIB is prepared by subjecting the compound of the Formula IIA to partial hydrogenation. Reduction is carried out by catalytic hydrogenation, preferably in the presence of a poisoned metal catalyst. One may preferably proceed by using a palladium catalyst poisoned by quinoline, calcium carbonate or lead acetate. It is particularly advantageous to use a catalyst poisoned by quinoline [Org. Synth. Coll. Vol. 3, 629 (1955)]. Partial hydrogenation may be preferably carried out at room temperature under atmospheric pressure. The reaction may be preferably accomplished in the presence of an inert organic solvent. As reaction medium advantageously a lower aliphatic alcohol (e.g. methanol or ethanol) may be used. The compound of the Formula IIB thus obtained can be isolated by known methods (e.g. by filtering the catalyst and evaporating the filtrate).

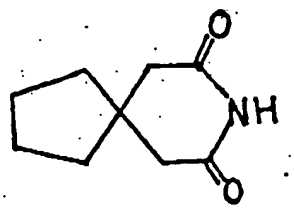
The compound of the general Formula II can be converted into an acid addition salt thereof by

methods known per se. For salt formation preferably pharmaceutically acceptable inorganic or organic acids can be used (e.g. hydrochloric acid, hydrogen bromide, sulfuric acid, nitric acid, or maleic acid, fumaric acid, lactic acid, malic acid, tartaric acid, succinic acid etc.). Salt formation may be advantageously performed by reacting the free base of the general Formula II with a molar equivalent amount of the corresponding acid in an inert organic solvent.

The compound of the general Formula II can be set free from an acid addition salt thereof in a manner known per se by treating with a suitable base.

The 8-aza-spiro[4.5]decane-7,9-dione-8--prop-2-ine of the Formula III used as starting material in the above procedures is a known compound.

According to a still further aspect of the present invention there is provided a process for the preparation of 8-aza-spiro[4.5]decane-7,9-dione--8-prop-2-ine of the Formula III which comprises reacting 8-aza-spiro[4.5]decane-7,9-dione of the Formula X



(X)

with a propargyl halide of the general Formula XI

$$Hal\text{-}CH_2\text{-}C{\equiv}CH \qquad (XI)$$

(wherein Hal stands for bromine, chlorine or iodine) in an inert solvent, in the presence of an acid binding agent.

It is known that the 8-aza-spiro[4.5]-decane-7,9-dione-8-prop-2-ine of the Formula III can be prepared by heating a mixture of 8-oxa-spiro[4.5]-decane-7,9-dione and propargyl amine in pyridine to boiling for 15 hours, evaporating the dilute reaction mixture and purifying the residue by distillation in vacuo [Yao-Gua Wu et al: J. Med. Chem. 12, 876-881 (1969)]. The compound of the Formula III is obtained with a yield of 76 %.

The above process is accompanied by several drawbacks which are particularly serious on industrial scale manufacture. The reaction time is very long (15 hours) and the temperature used is high (above 115 °C). The specific utilization of the volume of the reactor is unfavourable. The treatment, recovery and elimination of the pyridine used as solvent is problematic and comprises serious hazards of environmental pollution. A further disadvantage resides in the fact that propargyl amine used as starting material is a difficult-to-obtain expensive substance.

It is a further object of the

present invention to overcome the above drawbacks of the known procedures and to elaborate an economical process for the preparation of the compound of the Formula III which is favourably feasible on industrial scale as well.

The present invention is based on the recognition that on reacting 8-aza-spiro[4.5]decane-7,9-dione of the Formula X with a propargyl halide of the Formula XI the compound of the Formula III is obtained with good yields and in high purity in a readily feasible simple manner.

As compound of the general Formula XI preferably propargyl bromide may be used.

The starting materials of the Formulae X and XI can be used in equimolar amounts but the propargyl halide of the general Formula XI can be applied in a small - 10-20 molar % - excess as well.

The reaction can be carried out in any suitable inert organic solvent. As reaction medium any organic solvent can be used which does not enter into reaction with the components and does not influence the reaction in an adverse manner. It is preferred to use an ether (e.g. tetrahydrofuran, dioxane etc.), ester (e.g. ethyl acetate), nitrile (e.g. acetonitrile) or ketone (e.g. acetone or methyl ethyl ketone) or a mixture thereof as reaction medium.

The reaction is carried out in the presence of an acid binding agent. For this purpose preferably

an alkali carbonate (particularly sodium or potassium carbonate) can be used but other inorganic bases can be applied as well, e.g. an alkaline earth metal carbonate (e.g. calcium carbonate), an alkali hydrogen carbonate (e.g. sodium or potassium hydrogen carbonate), an alkali hydride (e.g. sodium hydride) or alkali amide (e.g. sodium amide etc.). Furthermore, tertiary organic bases can also be used as acid binding agent (e.g. trialkyl amines, such as triethyl amine).

The reaction temperature can vary between wide ranges. Thus one may generally work at 45-110 °C, preferably at 55-100 °C. The reaction temperature depends on the solvent used.

The reaction takes place very rapidly, the reaction time amounts to a few hours.

The reaction mixture can be worked up in a very simple manner. Thus, one may proceed by cooling the reaction mixture, removing the insoluble substances (alkali carbonate, alkali halide) by filtration or centrifuging and evaporating the filtrate. Thus, the compound of the Formula III is obtained in highly pure form which can be used for the further reactions directly without further purification. The sample of analytic purity of the product is obtained by fractional distillation in vacuo.

The advantages of the above process of the present invention can be summarized as follows:

- no long reaction time is required;

- the reaction can be accomplished at a temperature not exceeding 100 °C;
- no pyridine is used and therefore the difficulties which accompany the recovery and elimination of this solvent are overcome;
- the process is more favourable to the environment;
- the process is readily feasible on industrial scale, too;
- the specific utilization of the apparatus is favourable;
- the yield is very high;
- the desired compound of the Formula III is obtained in highly pure form and can be used for the further reaction directly, without further purification.

Further details of the process are to be found in the following Examples without limiting the scope of protection to the said Examples.

Preparation of the compound of Formula I

Example 1

8-{4-[4-(2-Pyrimidinyl)-1-piperazinyl]-butyl}-8-aza-spiro[4.5]decane-7,9-dione

To a solution of 38.15 g (0.1 mole) of 8-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-but-2-in-yl}-8-aza-spiro[4.5]decane-7,9-dione in 150 ml of ethanol 1 g of a palladium/charcoal catalyst is added, whereupon the mixture is hydrogenated under atmospheric pressure at room temperature under vigorous stirring until the hydrogen consumption stops (2 equivalents of hydrogen, about 5 litres). The catalyst is removed by

filtration and can be directly used in the next hydrogenation step. The filtrate is evaporated in vacuo. Thus 36.85 g of the desired compound are obtained, yield 95.6 %. M.p.: 91-99 °C (the melting point disclosed in prior art amounts to 90-98 °C).

Analysis for the Formula $C_{21}H_{31}N_5O_2$ (385.52)
calc.: C % = 65.43; H % = 8.11; N % = 18.17;
found: C % = 65.01; H % = 8.00; N % = 18.15.

The above base is converted into the hydrochloride by reacting with an equimolar amount of hydrogen chloride in ethanol. The hydrochloride melts at 200-202 °C (the melting point disclosed in prior art amounts to 201.5 - 202.5 °C).

Analysis for the formula $C_{21}H_{31}ClN_5O_2.HCl$ (421.98)
calc.: C % = 59.77; H % = 7.65; N % = 4.3; Cl^- %= 8.40;
found: C % = 59.51; H % = 7.50; N % = 4.26; Cl^- %= 8.37.

Preparation of the compound of the Formula IIA

Example 2

8-{4-[4-(2-Pyrimidinyl)-1-piperazinyl]-but-2-in-yl}-8-aza-spiro[4.5]decane-7,9-dione

Into a 250 ml round-bottomed flask equipped with a stirrer and reflux condenser 20.5 g (0.1 mole) of 8-aza-spiro[4.5]decane-7,9-dione-8-prop-2-ine, 25 ml of dioxane, 17.2 g (0.105 mole) of 1-(2-pyrimidinyl)-piperazine, 3.6 g of paraformaldehyde and 0.2 g of cupric(II)acetate are introduced. The reaction

mixture is heated to boiling for 3 hours, cooled to room temperature, poured into water and extracted three times with 50 ml of benzene each. The united benzene solutions are clarified with activated charcoal and evaporated on a hot water-bath. Thus 33.95 g of the desired compound are obtained, yield 89 %, m.p.: 78-80 °C (petrolether).

Analysis for the formula $C_{21}H_{27}N_5O_2$ (381.49)
calc.: C % = 66.12; H % = 7.13; N % = 18.36;
found: C % = 66.02; H % = 7.22; N % = 18.30.

Example 3

8-{4-[4-(2-Pyrimidinyl)-1-piperazinyl]-but-2-in-yl}-8-aza-spiro[4.5]decane-7,9-dione

A Grignard compound is prepared from 15.6 g (0.11 mole) of methyl iodide and 2.68 g (0.11 g-atom) of magnesium in 170 ml of anhydrous ether, whereupon a solution of 20.5 g (0.1 mole) of 8-aza-spiro[4.5]-decane-7,9-dione-8-prop-2-ine and 50 ml of anhydrous ether is added dropwise under vigorous stirring. The reaction mixture is heated to boiling until the development of methane gas comes to an end, whereupon 3 g (0.1 mole) of trioxymethylene (or 0.1 mole of anhydrous gaseous fromaldehyde) are added. The reaction mixture is heated to boiling for a further period of 4 hours and thereafter poured into a solution of 10 g of ammonium chloride and 35 ml of icecold water. The etheral solution is spearated, dried over anhydrous

magnesium sulfate and evaporated.

The oily residue (22.8 g, 96 %) is admixed without further purification with a suspension of 3.9 g (0.1 mole) of sodium amide and 70 ml of anhydrous benzene, whereupon, after the termination of the evolution of ammonia gas, at room temperature 19 g (0.1 mole) of p-toluene-sulfonyl chloride are added. The addition having been completed the reaction mixture is stirred at room temperature for some hours and washed successively with 40 ml of water, 40 ml of a saturated sodium bicarbonate solution and 40 ml of water, and dried over anhydrous magnesium sulfate. To the benzene solution 17.2 g (0.105 mole) of 1-(2-pyrimidinyl)-piperazine are added and the reaction mixture is heated to boiling for some hours. The reaction mixture is washed with an aqueous sodium bicarbonate solution and water, the benzene solution is evaporated in vacuo. The residue is taken up in petrolether and the crystals are filtered. Thus 23.65 g of the desired compound are obtained in the form of white crystals, yield 62 %, m.p.: 78-79 °C.

Analysis for the Formula $C_{21}H_{27}N_5O_2$ (381.49)

calc.: C % = 66.12; H % = 7.13; N % = 18.36;

found: C % = 65.85; H % = 7.02; N % = 18.10.

Preparation of the compound of the Formula IIB

Example 4

8-{4-[4-(2-Pyrimidinyl)-1-piperazinyl]-but-2-yl}-8-aza-spiro[4.5]decane-7,9-dione

Into a hydrogenating apparatus 38.15 g (0.1 mole) of 8-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-but-2-in-yl}-8-aza-spiro[4.5]decane-7,9-dione, 150 ml of ethanol, 1 g of a palladium/charcoal catalyst and 1 ml of "Quinoline S" deactivator are weighed in. The reaction mixture is hydrogenated at room temperature until the theoretical hydrogen amount (1 molar equivalent) is taken up. The catalyst is filtered and the filtrate is evaporated. Thus 37.2 g of the desired compound are obtained, yield 97 %.

Analysis for the Formula $C_{21}H_{29}N_5O_2$ (383.5)

calc.: C % = 65.77; H % = 7.62; N % = 18.26;

found: C % = 65.18; H % = 7.47; N % = 18.15.

Preparation of the compound of the Formula III

Example 5

8-Aza-spiro[4.5]decane-7,9-dione-8-prop-2-ine

Into a round-bottomed flask equipped with a stirrer, dropping funnel and reflux condenser a mixture of 167.2 g (1.0 mole) of 8-aza-spiro[4.5]-decane-7,9-dione, 130.86 g (1.1 moles) of propargyl bromide, 138.2 g (1.0 mole) of potassium carbonate

and 250 ml of acetonitrile are added. The reaction mixture is heated to boiling under stirring for some hours, then cooled to room temperature, filtered and the solvent is removed. Thus 178.6 g of the desired compound are obtained, yield 87 %, b.p.: 150 °C/53.31 Pa. Colourless viscous oil.

Analysis for the Formula $C_{12}H_{15}NO_2$ (205.26)

calc.: C % = 70.22; H % = 7.36; N % = 6.82;

found: C % = 71.10; H % = 7.42; N % = 6.80.

Example 6

One proceeds according to Example 5 except that potassium carbonate is replaced by 105.9 g (1.0 mole) of sodium carbonate. Thus 162.2 g of the product defined in Example 5 are obtained, yield 79 %, b.p.: 150 °C/53.31 Pa.

Example 7

One proceeds according to Example 5 except that acetonitrile is replaced by 250 ml of tetrahydrofurane. Thus 149.84 g of the product according to Example 5 are obtained, yield 73 %, b.p.: 150 °C/53.31 Pa.

Example 8

One proceeds according to Example 5 except that acetonitrile is replaced by 240 ml of dioxane. Thus 170.4 g of the product according to Example 5 are obtained, yield 83 %, b.p.: 150 °C/53.32 Pa.

Example 9

One proceeds according to Example 5 except that acetonitrile is replaced by 320 ml of ethyl acetate. Thus 145.7 g of the product according to Example 5 are obtained, yield 71 %, b.p.: 150 °C/53.32 Pa.

Example 10

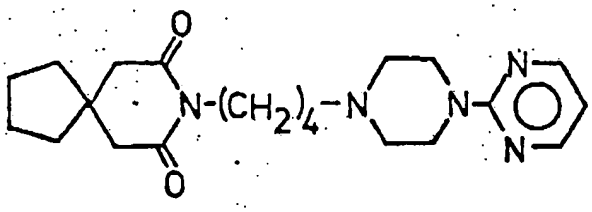
One proceeds according to Example 5 except that acetonitrile is replaced by 290 ml of acetone. Thus 153.95 g of the product according to Example 5 are obtained, yield 75 %, b.p.: 150 °C/53.32 Pa.

Example 11

One proceeds according to Example 5 except that acetonitrile is replaced by 250 ml of methyl ethyl ketone. Thus 178.6g of the product according to Example 5 are obtained, yield 87 %, b.p.: 150 °C/53.32 Pa.

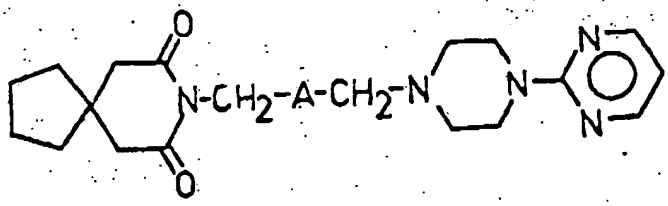
CLAIMS

1) Process for the preparation of 8-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-8-aza-spiro[4.5]decane-7,9-dione of the Formula I



(I)

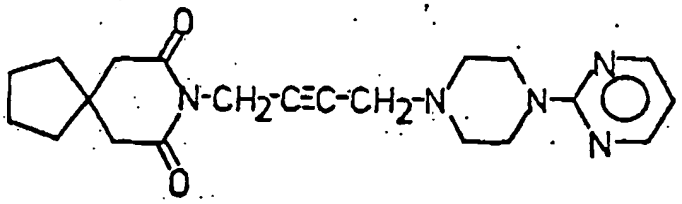
and pharmaceutically acceptable acid addition salts thereof, which comprises hydrogenating a compound of the general Formula II



(II)

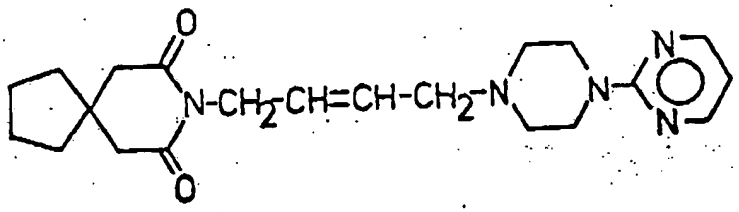
(wherein A stands for -C≡C- or -CH=CH-) and, if desired, converting the compound of the Formula I thus obtained into a pharmaceutically acceptable acid addition salt thereof.

2) Process according to Claim 1, which comprises hydrogenating the compound of the Formula IIA.



(IIA)

3) Process according to Claim 1, which comprises hydrogenating the compound of the Formula IIB.



(IIB)

4) Process according to Claim 1 or 2, which comprises hydrogenating the compound of the Formula IIA in the presence of a metal catalyst.

5) Process according to Claim 4, which comprises using a palladium or Raney-nickel catalyst.

6) Process according to Claim 5, which comprises carrying out hydrogenation under atmospheric pressure at room temperature.

7) Process according to Claim 6, which comprises carrying out hydrogenation in the presence of an inert organic solvent.

8) Process according to Claim 7, which c o m p r i s e s using a lower aliphatic alcohol - preferably methanol or ethanol - as inert organic solvent.

9) Process according to Claim 1 or 3, which c o m p r i s e s hydrogenating the compound of the general Formula IIB in the presence of a metal catalyst.

10) Process according to Claim 9, which c o m p r i s e s using a palladium catalyst.

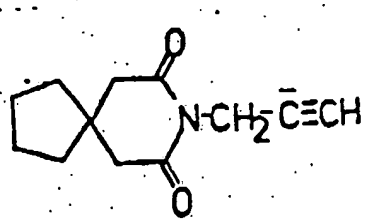
11) Compounds of the general Formula II wherein A stands for -C≡C- or -CH=CH- and acid addition salts thereof.

12) Compound of the Formula IIA and acid addition salts thereof.

13) Compound of the Formula IIB and acid addition salts thereof.

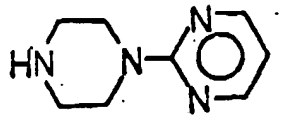
14) Process for the preparation of compounds of tne general Formula II (wherein A stands for -C≡C- or -CH=CH-) and acid addition salts thereof, which c o m p r i s e s

a) for the preparation of the compound of the Formula IIA, subjecting the propine derivative of the Formula III



(III)

to Mannich condensation with an amine of the Formula IV;



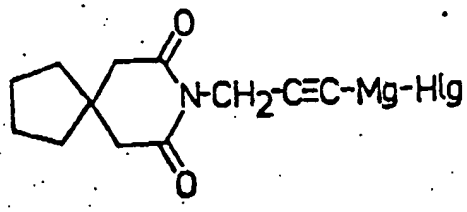
(IV)

or

b) for the preparation of the compound of Formula IIA, reacting the propine derivative of the Formula III with an alkyl magnesium halide of the general Formula V

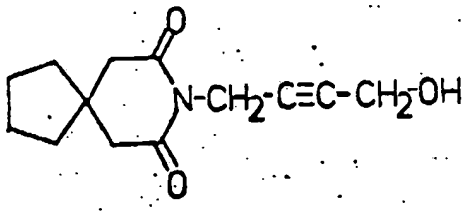
R-Mg-Hlg (V)

(wnerein R stands for C_{1-4} alkyl and Hlg is chlorine, iodine or bromine), reacting the compound of the general Formula VI



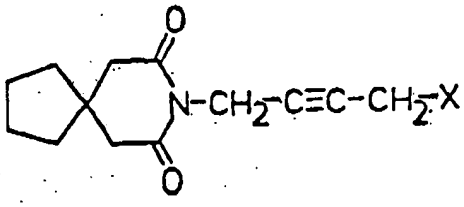
(VI)

thus obtained (wherein Hlg is as stated above) with at least one molar equivalent amount of trioxymethylene or formaldehyde, converting the substituted amino alcohol of the Formula VII thus obtained



(VII)

into a reactive ester of the general Formula VIII



(VIII)

(wherein X stands for a reactive ester group) and reacting the compound of the general Formula VIII thus obtained with a piperazine derivative of the Formula IV; or

c) for the preparation of the compound of the Formula IIB, subjecting the compound of the Formula IIA to partial hydrogenation;

and, if desired, converting a compound of the general Formula II thus obtained into an acid addition salt thereof or setting free the same from an acid addition salt.

15) Process according to method a) of Claim 14, which comprises carrying out Mannich condensation by using paraformaldehyde.

16) Process according to Claim 15, which c o m p r i s e s carrying out the reaction under heating, preferably at the boiling point of the reaction mixture.

17) Process according to any of Claim 14a , 15 and 16, which c o m p r i s e s carrying out the reaction in an inert organic solvent, preferably an ether, particularly dioxane.

18) Process according to method b) of Claim 14, which c o m p r i s e s using as alkyl magnesium halide of the general Formula V methyl magnesium iodide, methyl magnesium bromide, methyl magnesium chloride, ethyl magnesium iodide, ethyl magnesium chloride or ethyl magnesium bromide.

19) Process according to Claim 18, which c o m p r i s e s carrying out the reaction of the compounds of the Formulae III and V in ethereal medium under heating.

20) Process according to method b) of Claim 14, which c o m p r i s e s reacting the compound of the general Formula VI with trioxymethylene or gaseous formaldehyde under heating.

21) Process according to Claim 20, which c o m p r i s e s using trioxy methylene or formaldehyde in an amount of 1 - 1.1 moles - preferably 1 - 1.05 moles - related to 1 mole of the compound of the general Formula VI.

22) Process according to method b) of Claim 14, which c o m p r i s e s converting a compound of the Formula VII into an ester of the general Formula VIII, wherein X stands for halogen, alkylsulfonyloxy or arylsulfonyloxy.

23) Process according to Claim 22, which c o m p r i s e s preparing an ester of the general Formula VIII wherein X stands for chlorine, bromine, iodine, mesyloxy, phenylsulfonyloxy, p-bromo-phenylsulfonyloxy or tosyloxy.

24) Process according to Claim 22 or 23, which c o m p r i s e s reacting the compound of the Formula VII with p-toluene-sulfonyl chloride.

25) Process according to method b) of Claim 14, which c o m p r i s e s reacting a compound of the general Formula VIII with the piperazine derivative of the general Formula IV in an inert organic solvent - preferably an aromatic hydrocarbon, particularly benzene, toluene or xylene - under heating.

26) Process according to method c) of Claim 14, which c o m p r i s e s hydrogenating the compound of the Formula IIA with hydrogen in the presence of a poisoned catalyst to the compound of the Formula IIB.

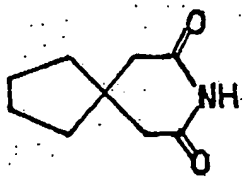
27) Process according to Claim 26, which c o m p r i s e s using a palladium catalyst poisoned with quinoline, calcium carbonate or lead acetate.

28) Process according to Claim 26 or 27, which c o m p r i s e s carrying out partial hydrogenation at room temperature under atmospheric pressure.

29) Process according to any of Claims 26 to 28, which c o m p r i s e s carrying out partial hydrogenation in a lower aliphatic alcohol as medium, preferably in methanol or ethanol.

30) Pharmaceutical compositions c o m p r i s i n g as active ingredient a compound of the general Formula II (wherein A stands for -C≡C- or -CH=CH-) or a pharmaceutically acceptable acid addition salt thereof in admixture with suitable inert pharmaceutical carriers.

31) Process for the preparation of 8-aza-spiro[4.5]decane-7,9-dione-8-prop-2-ine of the Formula III, which c o m p r i s e s reacting 8-aza-spiro[4.5]decane-7,9-dione of the Formula X



(X)

with a propargyl halide of the general Formula XI,

$$Hal\text{-}CH_2\text{-}C{\equiv}CH \quad - \qquad (XI)$$

wherein Hal stands for bromine, chlorine or iodine in an inert solvent, in the presence of an acid binding agent.

32) Process according to Claim 31, which comprises using propargyl bromide as compound of the general Formula XI.

33) Process according to Claim 31 or 32, which comprises using an ether, ester, nitrile or ketone as inert solvent.

34) Process according to Claim 33, which comprises using tetrahydrofurane, dioxane, ethyl acetate, acetonitrile, acetone or methyl ethyl ketone as inert organic solvent.

35) Process according to any of Claims 31 to 34, which comprises using an alkali metal carbonate - preferably sodium or potassium carbonate - as acid binding agent.

36) A process as claimed in claim 1 substantially as hereinbefore described in Example 1.

37) A process as claimed in claim 14 substantially as hereinbefore described in any one of Examples 2, 3 or 4.

38) A process as claimed in claim 31 substantially as hereinbefore described in any one of Examples 5 to 11.

39. A compound of the general formula I prepared by a process as claimed in any one of claims 1 to 10 or 36.

40. A compound of the general formula II where A is defined in claim 1 prepared by a process as claimed in any one of claims 14 to 29 or 37.

41. A compound of the general formula III prepared by a process as claimed in any one of claims 31 to 34 or 38.

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